

## Original Investigation

# Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease

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**IMPORTANCE** Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular disease (CVD) compared with the general population. Prior studies have produced contradictory results on the association of dietary sodium intake with risk of CVD, and this relationship has not been investigated in patients with CKD.

**OBJECTIVE** To evaluate the association between urinary sodium excretion and clinical CVD events among patients with CKD.

**DESIGN, SETTING, AND PARTICIPANTS** A prospective cohort study of patients with CKD from 7 locations in the United States enrolled in the Chronic Renal Insufficiency Cohort Study and followed up from May 2003 to March 2013.





**EXPOSURES** The cumulative mean of urinary sodium excretion from three 24-hour urinary measurements and calibrated to sex-specific mean 24-hour urinary creatinine excretion.

**MAIN OUTCOMES AND MEASURES** A composite of CVD events defined as congestive heart failure, stroke, or myocardial infarction. Events were reported every 6 months and confirmed by medical record adjudication.

**RESULTS** Among 3757 participants (mean age, 58 years; 45% women), 804 composite CVD events (575 heart failure, 305 myocardial infarction, and 148 stroke) occurred during a median 6.8 years of follow-up. From lowest (<2894 mg/24 hours) to highest ( $\geq$ 4548 mg/24 hours) quartile of calibrated sodium excretion, 174, 159, 198, and 273 composite CVD events occurred, and the cumulative incidence was 18.4%, 16.5%, 20.6%, and 29.8% at median follow-up. In addition, the cumulative incidence of CVD events in the highest quartile of calibrated sodium excretion compared with the lowest was 23.2% vs 13.3% for heart failure, 10.9% vs 7.8% for myocardial infarction, and 6.4% vs 2.7% for stroke at median follow-up. Hazard ratios of the highest quartile compared with the lowest quartile were 1.36 (95% CI, 1.09-1.70;  $P = .007$ ) for composite CVD events, 1.34 (95% CI, 1.03-1.74;  $P = .03$ ) for heart failure, and 1.81 (95% CI, 1.08-3.02;  $P = .02$ ) for stroke after multivariable adjustment. Restricted cubic spline analyses of the association between sodium excretion and composite CVD provided no evidence of a nonlinear association ( $P = .11$ ) and indicated a significant linear association ( $P < .001$ ).

**CONCLUSIONS AND RELEVANCE** Among patients with CKD, higher urinary sodium excretion was associated with increased risk of CVD.

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Chronic kidney disease (CKD) affects approximately 11% of the US general population<sup>1</sup> and is associated with increased risk of end-stage renal disease, cardiovascular disease (CVD), and all-cause mortality.<sup>2,3</sup> Greater than 1 in 3 US adults has CVD, and it is the leading cause of death in the United States.<sup>4</sup> Those with CKD are at increased risk of CVD compared with those with normal kidney function, and risk increases as CKD progresses.<sup>2,3</sup>

A positive association between sodium intake and blood pressure is well established.<sup>5</sup> However, the association between sodium intake and clinical CVD remains less clear.<sup>6</sup> While some studies reported a J- or U-shaped association between dietary sodium and CVD,<sup>7,8</sup> others found a positive monotonic association between sodium intake and risk of CVD, coronary heart disease, congestive heart failure (CHF), and stroke.<sup>9-11</sup> Methodologic limitations, including inconsistencies in dietary sodium measurement methods, could contribute to these conflicting findings.<sup>6</sup>

Blood pressure of patients with CKD is more sensitive to high sodium intake than persons with normal kidney function due to a diminished capacity to excrete sodium.<sup>12</sup> Despite this, there is limited prior research on the association between dietary sodium intake and CVD among those with impaired kidney function,<sup>13,14</sup> and to our knowledge, no previous studies have examined the association between sodium intake and incident CVD among patients with CKD. In addition, few studies examining the association between dietary sodium and CVD have used the mean of multiple 24-hour urine samples to quantify urinary sodium excretion, which is considered the best method for estimating usual sodium intake.<sup>6,15</sup> The objective of this study was to determine the prospective relationship between urinary sodium (and potassium) excretion, estimated from the mean of 3 repeated 24-hour urine samples, and risk of clinical CVD among patients with CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

## Methods

### Study Participants

The CRIC Study is an ongoing, multicenter, prospective cohort study of adults aged 21 to 74 years with mild to moderate CKD designed to identify and examine risk factors for CKD progression and development of CVD in those with CKD. Details of the CRIC Study design and methods have been published previously.<sup>16</sup> Briefly, a total of 3939 racially and ethnically diverse participants, approximately half of whom had diabetes, were recruited from 7 clinical centers in the United States from 2003 to 2008. Participants were eligible for the study if they met age-specific estimated glomerular filtration rate (eGFR) criteria of 20 to 70 mL/min/1.73 m<sup>2</sup>. Those with a history of kidney transplant, dialysis for at least 1 month, glomerulonephritis requiring immunosuppression, advanced heart failure, cirrhosis, or polycystic kidney disease were ineligible.

Institutional review boards at all participating institutions approved the study protocol, and the study adhered to

the Declaration of Helsinki. All participants provided written informed consent.

### Measurements

Self-reported sociodemographic and lifestyle characteristics, medical history, current medication use, and responses to a food frequency questionnaire,<sup>17</sup> which was used to estimate total calorie intake, were obtained at the baseline visit. Race was self-reported in response to questions with fixed categories and was used to calculate eGFR to determine eligibility. Blood pressure, height, weight, and waist circumference were measured using standard protocols, and fat-free mass was obtained by bioelectrical impedance analysis.<sup>16,18</sup> An overnight fasting blood sample was collected to measure serum creatinine, lipids, and plasma glucose. Serum creatinine measurements were calibrated to isotope dilution mass spectrometry traceable values. Hypertension was defined as mean blood pressure of 140/90 mm Hg or greater or self-reported use of antihypertensive medication, and diabetes was defined as a fasting plasma glucose of 126 mg/dL or greater, a nonfasting plasma glucose 200 mg/dL or greater, or self-reported use of antidiabetes medication. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation, which includes serum creatinine, age, sex, and race.<sup>1</sup>

Study participants were requested to collect 24-hour urine specimens at baseline and the first 2 annual follow-up visits. If either the total urine volume was less than 500 mL at the end of 24 hours or the duration of collection was not between 22 and 24 hours, participants were instructed to recollect the urine sample. Urinary sodium and potassium levels were measured by flame emission spectrophotometry (Instrumentation Laboratory Flame Photometer model 943). Urinary creatinine was measured on a BioTek Plate Reader ELx808 using a Jaffe reaction with a colorimetric end point and reagents from Sigma-Aldrich. All laboratory analyses were conducted at the CRIC Study central laboratory at the University of Pennsylvania with stringent quality control.

The cumulative mean of 24-hour urinary sodium excretion obtained from the baseline visit and the first 2 annual follow-up visits prior to developing a study event was calculated as the exposure variable. This approach was selected to take full advantage of all available exposure and outcome data.<sup>19</sup> Twenty-four-hour urinary sodium excretion was calibrated according to the sex-specific mean of 24-hour urinary creatinine excretion in the study population (1569 mg/24 hours in men and 1130 mg/24 hours in women) in order to reduce measurement error due to potential incompleteness of 24-hour urine collection. Calibration was done by multiplying each sample's urinary sodium-to-creatinine ratio by sex-specific mean creatinine level in the study population. Uncalibrated mean 24-hour urinary sodium excretion was also used as an exposure variable in sensitivity analyses.

### Outcome Assessment

Study participants attended annual clinic visits and received telephone calls every 6 months between in-person visits. Cardiovascular clinical outcomes were assessed using a standard

medical event questionnaire at all follow-up contacts. Medical records were requested for event verification, and 2 physicians adjudicated each cardiovascular event and classified them as either probable or definite.<sup>16</sup>

The primary outcome of interest was composite CVD, defined as the first of CHF, myocardial infarction (MI), and stroke that occurred during follow-up. In addition, CHF, MI, and stroke were analyzed individually. All included CVD events were nonfatal. Congestive heart failure was identified by hospital admission for new or worsening CHF signs and symptoms, in addition to diminished cardiac output. Myocardial infarction was defined by characteristic changes in troponin and creatine kinase-MB levels, symptoms of myocardial ischemia, electrocardiogram changes, or new fixed perfusion abnormalities. Stroke was defined as rapid onset of neurologic deficit, headache, or other nonvascular cause and clinically relevant lesion on brain imaging for longer than 24 hours or death within 24 hours. All events classified as probable or definite during adjudication were included in these analyses. Follow-up was censored at the first of either death, loss to follow-up, withdrawal, or March 2013.

### Statistical Analysis

Baseline characteristics of study participants were compared across quartiles of calibrated urinary sodium excretion using  $\chi^2$  tests for categorical variables and analysis of variance and Kruskal-Wallis tests for normally and nonnormally distributed continuous variables, respectively.

Cumulative incidence of composite CVD, CHF, MI, and stroke were calculated by quartile of urinary sodium excretion using the Kaplan-Meier method and compared using the log-rank test with the null hypothesis that the cumulative incidence was the same among quartiles of sodium excretion.<sup>20</sup> Hazards ratios for the associations of urinary sodium excretion with composite CVD, CHF, MI, and stroke were estimated using Cox proportional hazards models with follow-up time used as the time scale.<sup>21</sup> The assumption of proportionality was tested using Schoenfeld residuals and interaction terms with time for each exposure variable and covariate. No substantial deviations from proportionality were observed. Complete case analysis was used for the main findings. Multiple imputation for missing covariate values was performed in a sensitivity analysis, and no substantial differences were observed. Urinary sodium excretion was analyzed in quartiles and as a continuous variable.

Analyses of subgroups defined by sex, age, race, diabetes status, and history of CVD were performed, and effect modification was assessed by including interaction terms with calibrated sodium excretion in the models. Important covariates for CVD were selected based on prior knowledge and were adjusted in multivariable analyses. First, unmodifiable demographic risk factors, ie, age, sex, race, and CRIC clinic site, were adjusted in the multivariable models (model 1). Next, established modifiable CVD risk factors were added to the multivariable models (model 2): education, waist circumference, lean body mass index, body mass index, cigarette smoking, alcohol drinking, physical activity, low-density lipoprotein cholesterol level, glucose level, history of CVD, use of antidia-

betic and lipid-lowering medications, use of diuretics, use of renin-angiotensin system blocking agents and other antihypertensive medications, and urinary creatinine. Finally, eGFR at baseline was included in the multivariable models (model 3). Systolic blood pressure was not adjusted in the main analyses because blood pressure might be on the causal pathway between urinary sodium excretion and CVD events.<sup>6</sup> However, systolic blood pressure was adjusted in sensitivity analyses. In addition, because 24% of participants were missing data on total caloric intake, total caloric intake was not adjusted in the primary analyses but was adjusted in sensitivity analyses.

Possible nonlinear relationships between urinary sodium excretion and composite CVD, CHF, MI, and stroke were examined with restricted cubic splines.<sup>22</sup> Analyses were multivariable-adjusted and used 3 knots, and the 2.5% highest and lowest sodium excretion observations were trimmed. Knots were located at the 5%, 50%, and 95% percentiles corresponding to values of calibrated urinary sodium excretion of 2175, 3636, and 6017 mg/d, respectively. Sensitivity analyses were conducted using alternate middle knot locations of 3800 and 4000 mg/d based on biologic plausibility, as well as using 4 or 5 knots instead of 3 knots. Tests for nonlinearity comparing a model with only the linear term to a model with the linear and restricted cubic spline terms were conducted using likelihood ratio tests. If a test for nonlinearity was not significant, a test for linearity was conducted comparing a model with the linear term to a model with only the covariates of interest.

All analyses were also conducted with urinary potassium excretion as the exposure of interest using the same methodologic approach described above. All analyses were conducted using SAS version 9.2, and all hypothesis testing was 2-tailed with  $P < .05$  set as statistically significant.

## Results

A total of 3757 participants (mean age, 58 years; 45% women) were included in this analysis. Participants with incomplete or missing 24-hour urine collection were excluded ( $n = 182$ ): 54 participants who did not successfully collect any 24-hour urine specimens, 126 participants with incomplete 24-hour urine collection (3 with total urine volume  $<500$  mL, 10 with collection duration  $<20$  hours, and 113 with total creatinine excretion  $<7$  mg/kg of body weight), and 2 participants with mean urinary sodium excretion less than 20 mmol/24 hours. A total of 2167 participants had 3 sodium measurements, 982 had 2 measurements, and 608 had only 1 measurement. There was no significant difference in mean urinary sodium excretion between those with all 3 measurements and those with fewer (mean [SD], 3725 [1328] mg/24 hours vs 3669 [1586] mg/24 hours;  $P$  for difference = .24).

Overall, mean (SD) 24-hour sodium excretion was 3701 (1443) mg. Participants with higher calibrated 24-hour urinary sodium excretion were more likely to be male, white, and current smokers; report a history of hypertension, diabetes, hypercholesterolemia, and CVD; and take antihypertensive medications (Table 1). Those with the highest sodium excretion also had the highest systolic and diastolic blood pressure;

**Table 1. Characteristics of 3757 Patients With Chronic Kidney Disease According to Quartile of Calibrated 24-Hour Urinary Sodium Excretion: Chronic Renal Insufficiency Cohort Study**

Variable	Calibrated Urinary Sodium Excretion, mg/24 h <sup>a</sup>				P Value
	<2894 (n = 939)	2894-3649 (n = 940)	3650-4547 (n = 939)	≥4548 (n = 939)	
Age, mean (SD), y	57.2 (10.9)	57.7 (11.3)	58.2 (10.8)	58.0 (10.6)	.24
Men, No. (%)	329 (35.0)	469 (49.9)	576 (61.3)	714 (76.0)	<.001
Race/ethnicity, No. (%)					
White	362 (38.6)	429 (45.6)	475 (50.6)	510 (54.3)	
Black	483 (51.4)	414 (44.0)	351 (37.4)	309 (32.9)	<.001
Other	94 (10.0)	97 (10.3)	113 (12.0)	120 (12.8)	
High school graduate, No. (%)	762 (81.2)	751 (79.9)	760 (80.9)	737 (78.5)	.44
Current smoking, No. (%)	120 (12.8)	95 (10.1)	110 (11.7)	155 (16.5)	<.001
Weekly alcohol drinking, No. (%)	220 (23.4)	233 (24.8)	261 (27.8)	254 (27.1)	.11
Physical activity, mean (SD), METs/wk	190.5 (130.3)	201.7 (144.4)	206.5 (155.3)	197.9 (146.9)	.11
Hypertension, No. (%)	753 (80.2)	813 (86.5)	814 (86.7)	853 (90.8)	<.001
Diabetes, No. (%)	354 (37.7)	412 (43.8)	463 (49.3)	566 (60.3)	<.001
History of CVD, No. (%)	256 (27.3)	282 (30.0)	328 (34.9)	373 (39.7)	<.001
Antihypertensive medication, No. (%)	807 (86.5)	856 (92.0)	873 (93.6)	890 (95.4)	<.001
Diuretics	528 (56.6)	537 (57.7)	531 (56.9)	608 (65.2)	<.001
RAS blocking agents	564 (60.5)	677 (72.8)	664 (71.2)	662 (71.0)	<.001
Other antihypertensive medications	611 (65.5)	628 (67.5)	677 (72.6)	711 (76.2)	<.001
Lipid-lowering medication, No. (%)	491 (52.6)	536 (57.6)	601 (64.4)	609 (65.3)	<.001
Antidiabetic medication, No. (%)	310 (33.2)	372 (40.0)	422 (45.2)	508 (54.4)	<.001
Systolic BP, mean (SD), mm Hg	125.7 (21.7)	126.3 (20.9)	128.1 (21.7)	132.3 (22.4)	<.001
Diastolic BP, mean (SD), mm Hg	70.7 (12.7)	71.0 (12.8)	71.4 (12.3)	72.7 (13.0)	.006
Waist circumference, mean (SD), cm	104.4 (18.5)	105.1 (16.8)	106.0 (17.1)	107.2 (17.2)	.004
Body mass index, mean (SD) <sup>b</sup>	31.7 (8.0)	32.1 (7.5)	31.9 (7.3)	31.8 (7.5)	.70
Lean body mass index, mean (SD) <sup>c</sup>	20.0 (4.1)	20.7 (3.8)	21.3 (4.3)	22.0 (4.2)	<.001
Daily total calorie intake, mean (SD), kcal	1745 (744)	1792 (790)	1853 (824)	1948 (905)	<.001
LDL cholesterol, mean (SD), mg/dL	105.3 (36.5)	103.9 (34.2)	101.2 (35.5)	99.0 (35.3)	<.001
HDL cholesterol, mean (SD), mg/dL	49.7 (16.5)	48.3 (16.0)	46.7 (14.5)	45.3 (14.5)	<.001
Triglycerides, mean (SD), mg/dL	147.0 (119.4)	156.0 (123.5)	158.9 (113.7)	164.1 (107.5)	.01
Glucose, mean (SD), mg/dL	109.2 (46.9)	111.4 (49.5)	113.6 (46.5)	124.0 (55.8)	<.001
HbA <sub>1c</sub> , mean (SD), %	6.4 (1.4)	6.6 (1.6)	6.6 (1.4)	6.9 (1.7)	<.001
Urinary creatinine, mean (SD), mg/24 h	1384 (490)	1404 (472)	1410 (474)	1298 (417)	<.001
Urinary sodium, mean (SD), mg/24 h	2491 (870)	3364 (925)	4008 (1096)	4941 (1518)	<.001
Urinary potassium, mean (SD), mg/24 h	2003 (854)	2065 (820)	2223 (1052)	2352 (984)	<.001
Calibrated sodium excretion, mean (SD), mg/24 h <sup>a</sup>	2345 (436)	3278 (216)	4065 (249)	5776 (1361)	<.001
Calibrated potassium excretion, mean (SD), mg/24 h <sup>a</sup>	1960 (862)	2061 (777)	2288 (909)	2745 (1038)	<.001
Urinary protein, median (IQR), g/24 h	0.11 (0.06-0.53)	0.12 (0.07-0.57)	0.20 (0.08-0.85)	0.49 (0.11-1.94)	<.001
eGFR, mean (SD), mL/min/1.73 m <sup>2</sup>	45.4 (15.9)	45.5 (14.5)	44.0 (14.9)	42.9 (14.1)	<.001

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA<sub>1c</sub>, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; METs, metabolic equivalents; RAS, renin-angiotensin system.

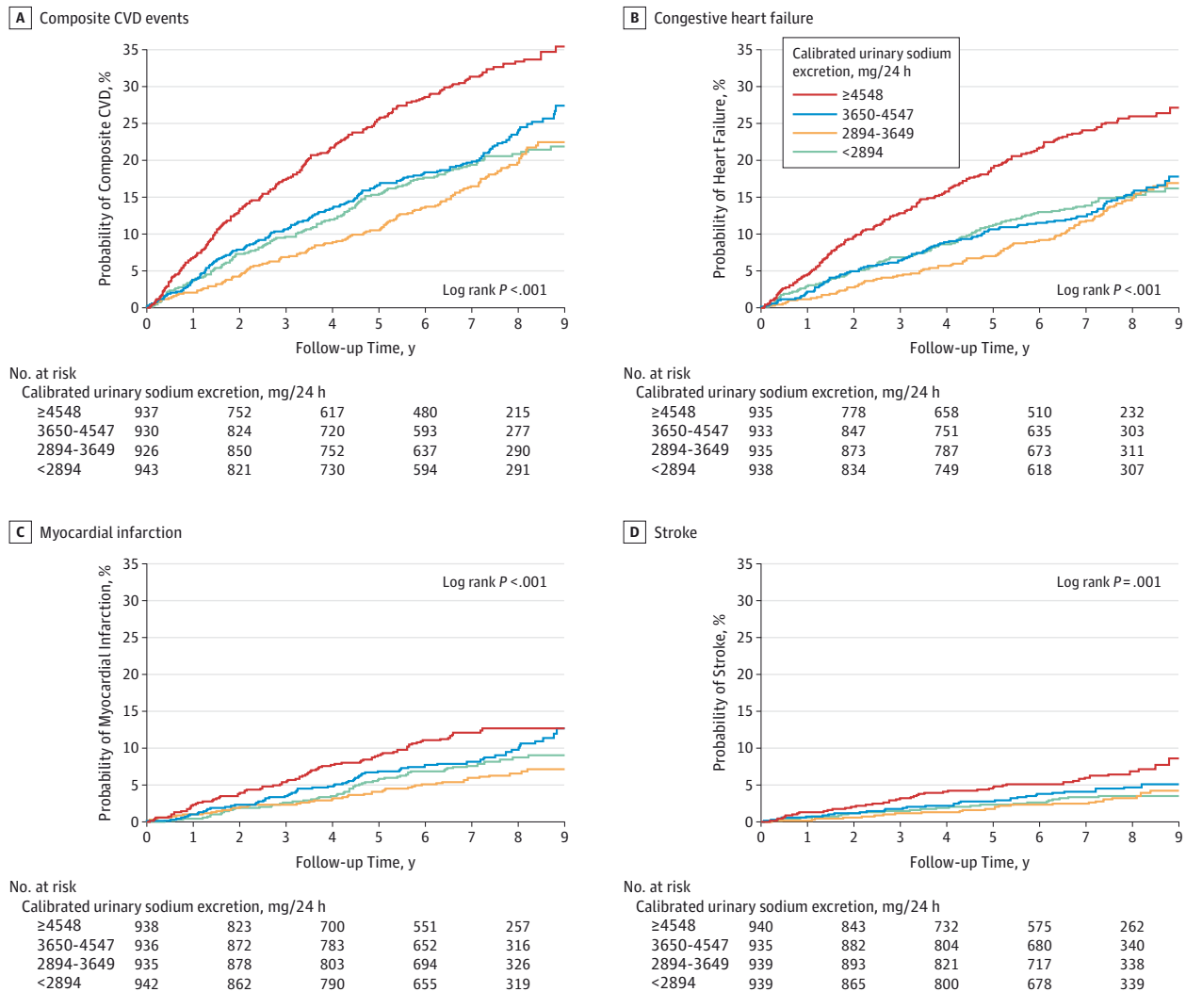
SI conversion factors: To convert LDL and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; and glucose to mmol/L, multiply by 0.0555.

<sup>a</sup> Calibrated to mean urinary creatinine excretion of 1569 mg/24 hours in men and 1130 mg/24 hours in women.

<sup>b</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>c</sup> Calculated as fat-free mass in kilograms divided by height in meters squared.

Figure 1. Cumulative Kaplan-Meier Estimates of Cardiovascular Diseases According to Quartile of Calibrated 24-Hour Urinary Sodium Excretion



Because participants who only had urinary sodium excretion measurements after an outcome occurred were excluded from the analysis for that outcome, there are slightly fewer people at time = 0 years for each individual outcome compared with the 3757 participants described in Table 1, who contributed to at least 1 outcome but not necessarily all of them.

waist circumference; lean body mass index; daily calorie intake; and triglycerides, glucose, and glycated hemoglobin levels and the lowest low-density and high-density lipoprotein cholesterol values. Urinary potassium and protein excretion levels were highest, while eGFR was lowest, in participants with the highest calibrated sodium excretion.

Over a median 6.8 years of follow-up, 804 composite first CVD events, 575 CHF events, 305 MI events, and 148 stroke events occurred, corresponding to incidence rates of 35.7 CVD events per 1000 person-years, 24.6 CHF events per 1000 person-years, 12.6 MI events per 1000 person-years, and 6.0 stroke events per 1000 person-years. From lowest (<2894 mg/24 hours) to highest (≥4548 mg/24 hours) quartile of calibrated sodium excretion, the cumulative incidence of composite CVD at median follow-up was 18.4%, 16.5%, 20.6%, and 29.8% (log-rank  $P < .001$ ); the cumulative incidence of CHF was 13.3%, 12.0%, 13.3%, and 23.2% (log-rank

$P < .001$ ); the cumulative incidence of MI was 7.8%, 5.8%, 8.6%, and 10.9% (log-rank  $P < .001$ ); and the cumulative incidence of stroke was 2.7%, 2.8%, 4.1%, and 6.4% (log-rank  $P = .001$ ), respectively (Figure 1 and Table 2).

After adjustment for age, sex, race, and clinic site, those in the highest quartile of calibrated urinary sodium excretion were at an increased risk for composite CVD, CHF, MI, and stroke compared with the lowest quartile of calibrated urinary sodium excretion (Table 2). After additional adjustment for modifiable CVD risk factors, calibrated sodium excretion remained significantly associated with composite CVD, CHF, and stroke but was no longer significantly associated with MI. In fully adjusted models, including adjustment for baseline eGFR, the highest quartile of urinary sodium excretion was significantly associated with composite CVD (hazard ratio [HR], 1.36 [95% CI, 1.09-1.70];  $P = .007$ ), CHF (HR, 1.34 [95% CI, 1.03-1.74];  $P = .03$ ), and stroke (HR, 1.81 [95% CI,

**Table 2. Composite Cardiovascular Disease, Congestive Heart Failure, Myocardial Infarction, and Stroke According to Quartile of Calibrated 24-Hour Urinary Sodium Excretion**

Variable	No. of Participants	Calibrated Urinary Sodium Excretion, mg/24 h <sup>a</sup>				P Value for Trend
		<2894	2894-3649	3650-4547	≥4548	
No. of participants		939	940	939	939	
<b>Composite CVD<sup>b</sup></b>						
Events		174	159	198	273	
Person-years		5804	5972	5739	5012	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		18.4 (15.8-20.9)	16.5 (14.1-18.8)	20.6 (18.0-23.1)	29.8 (26.7-32.7)	<.001
Model 1, HR (95% CI) <sup>d</sup>	3736	1 [Reference]	0.88 (0.71-1.10)	1.14 (0.93-1.41)	1.79 (1.46-2.19)	<.001
P value			.27	.22	<.001	
Model 2, HR (95% CI)	3528	1 [Reference]	0.85 (0.68-1.07)	0.99 (0.80-1.24)	1.31 (1.05-1.63)	.002
P value			.17	.96	.02	
Model 3, HR (95% CI)	3528	1 [Reference]	0.87 (0.69-1.10)	1.01 (0.81-1.26)	1.36 (1.09-1.70)	<.001
P value			.24	.96	.007	
<b>Congestive Heart Failure</b>						
Events		125	117	127	206	
Person-years		5938	6216	5998	5235	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		13.3 (11.0-15.5)	12.0 (9.9-14.0)	13.3 (11.1-15.4)	23.2 (20.3-26.0)	<.001
Model 1, HR (95% CI) <sup>d</sup>	3741	1 [Reference]	0.90 (0.70-1.16)	1.01 (0.78-1.30)	1.90 (1.50-2.41)	<.001
P value			.41	.96	<.001	
Model 2, HR (95% CI)	3533	1 [Reference]	0.86 (0.66-1.13)	0.83 (0.63-1.08)	1.27 (0.98-1.65)	.02
P value			.27	.16	.08	
Model 3, HR (95% CI)	3533	1 [Reference]	0.89 (0.68-1.17)	0.84 (0.65-1.11)	1.34 (1.03-1.74)	.008
P value			.40	.22	.03	
<b>Myocardial Infarction</b>						
Events		69	54	83	99	
Person-years		6195	6336	6175	5569	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		7.8 (6.0-9.7)	5.8 (4.3-7.3)	8.6 (6.8-10.3)	10.9 (8.7-12.9)	.002
Model 1, HR (95% CI) <sup>d</sup>	3751	1 [Reference]	0.73 (0.51-1.04)	1.10 (0.79-1.53)	1.42 (1.02-1.98)	.002
P value			.08	.57	.04	
Model 2, HR (95% CI)	3540	1 [Reference]	0.66 (0.44-0.97)	1.00 (0.70-1.43)	1.12 (0.77-1.62)	.14
P value			.03	.99	.56	
Model 3, HR (95% CI)	3540	1 [Reference]	0.66 (0.45-0.97)	1.00 (0.70-1.43)	1.15 (0.79-1.66)	.11
P value			.04	.99	.46	
<b>Stroke</b>						
Events		28	28	39	53	
Person-years		6293	6479	6337	5719	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		2.7 (1.6-3.7)	2.8 (1.7-3.8)	4.1 (2.8-5.3)	6.4 (4.6-8.1)	<.001
Model 1, HR (95% CI) <sup>d</sup>	3753	1 [Reference]	1.04 (0.61-1.77)	1.55 (0.94-2.54)	2.51 (1.55-4.07)	<.001
P value			.88	.09	<.001	
Model 2, HR (95% CI)	3542	1 [Reference]	0.92 (0.53-1.59)	1.38 (0.83-2.29)	1.80 (1.08-3.00)	.007
P value			.76	.21	.02	
Model 3, HR (95% CI)	3542	1 [Reference]	0.93 (0.54-1.61)	1.38 (0.83-2.29)	1.81 (1.08-3.02)	.006
P value			.79	.21	.02	

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.

<sup>a</sup> Calibrated to mean urinary creatinine excretion of 1569 mg/24 hours in men and 1130 mg/24 hours in women.

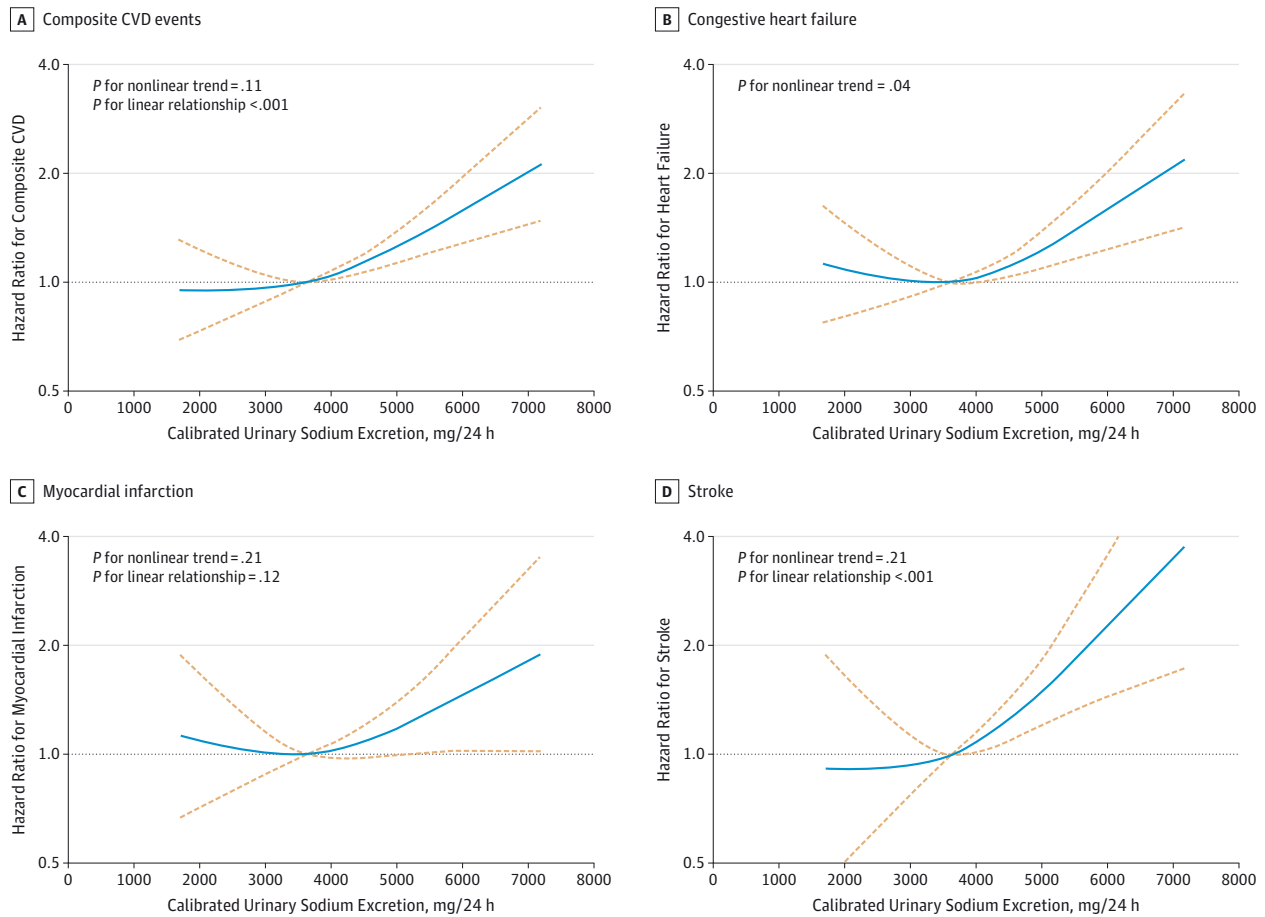
<sup>b</sup> Composite CVD is defined as congestive heart failure, stroke, and myocardial infarction.

<sup>c</sup> Adjusted for age, sex, race, and clinic site.

<sup>d</sup> Model 1: adjusted for age, sex, race, and clinic site. Model 2: model 1 plus

education; waist circumference; lean body mass index; body mass index; cigarette smoking; alcohol drinking; physical activity; low-density lipoprotein cholesterol; glucose; history of CVD; use of antidiabetic medications, lipid-lowering medications, diuretics, renin-angiotensin system blocking agents, and other antihypertensive medications; and urinary creatinine excretion. Model 3: model 2 plus adjustment for baseline estimated glomerular filtration rate.

**Figure 2. Multiple-Adjusted Hazard Ratios and 95% Confidence Intervals of Cardiovascular Diseases Associated With Calibrated 24-Hour Urinary Sodium Excretion**



Hazard ratios were adjusted for age, sex, race, clinic site, education, waist circumference, lean body mass index, body mass index, cigarette smoking, alcohol drinking, physical activity, low-density lipoprotein cholesterol, glucose, history of cardiovascular disease, antidiabetic medications, lipid-lowering

medications, diuretics, renin-angiotensin system blocking agents, other antihypertensive medications, urinary creatinine excretion, and baseline estimated glomerular filtration rate.

1.08-3.02];  $P = .02$ ), but not with MI (HR, 1.15 [95% CI, 0.79-1.66];  $P = .46$ ). Results for urinary sodium excretion not calibrated with urinary creatinine excretion were similar to those using calibrated urinary sodium excretion (eTable 1 in the Supplement). For example, compared with the lowest quartile of urinary sodium excretion (<2686 mg/24 hours), those in the highest quartile of urinary sodium excretion ( $\geq 4474$  mg/24 hours) were at an increased risk for composite CVD (HR, 1.35 [95% CI, 1.05-1.72];  $P = .02$ ), CHF (HR, 1.25 [95% CI, 0.94-1.67];  $P = .12$ ), MI (HR, 1.30 [95% CI, 0.87-1.95];  $P = .20$ ), and stroke (HR, 1.91 [95% CI, 1.08-3.33];  $P = .03$ ).

Multivariable-adjusted restricted cubic spline analyses suggested no evidence of a nonlinear association between calibrated urinary sodium excretion and composite CVD, MI, or stroke (Figure 2). They also indicated a significant linear association between calibrated urinary sodium excretion and composite CVD and stroke, but not with MI. There was no evidence of a nonlinear association between uncalibrated urinary sodium excretion and any CVD outcome

using restricted cubic spline analyses (eFigure 1 in the Supplement). There was evidence of a significant linear relationship between uncalibrated urinary sodium excretion and composite CVD ( $P = .002$ ), stroke ( $P = .02$ ), and MI ( $P = .048$ ).

Hazard ratios for composite CVD, CHF, MI, and stroke associated with a 1000-mg/24-hour increase in calibrated urinary sodium excretion were 1.10 (95% CI, 1.05-1.16;  $P < .001$ ), 1.09 (95% CI, 1.02-1.15;  $P = .005$ ), 1.07 (95% CI, 0.98-1.16;  $P = .11$ ), and 1.16 (95% CI, 1.05-1.28;  $P = .003$ ), respectively (Table 3). The magnitude of these associations was consistent across predefined subgroups of sex, race, age, and history of diabetes and CVD, although some did not reach statistical significance. In addition, no significant  $P$  values for interaction were observed for any of the subgroups of interest with calibrated sodium excretion. Sensitivity analyses that additionally adjusted for total calorie intake and systolic blood pressure did not substantially change the magnitude of any of the associations between a 1000-mg/24-hour

**Table 3. Composite Cardiovascular Disease, Congestive Heart Failure, Myocardial Infarction, and Stroke Associated With a 1000-mg Difference in Calibrated 24-Hour Urinary Sodium Excretion<sup>a</sup>**

Subgroups	Calibrated Urinary Sodium Excretion per 1000 mg/24 h <sup>b</sup>							
	No.	HR (95% CI)	P Value	P Value for Interaction	No.	HR (95% CI)	P Value	P Value for Interaction
	Composite CVD <sup>c</sup>				Congestive Heart Failure			
Overall	3528	1.10 (1.05-1.16)	<.001		3533	1.09 (1.02-1.15)	.005	
Sex				.55				.55
Men	1946	1.12 (1.06-1.18)	<.001		1949	1.10 (1.03-1.18)	.006	
Women	1582	1.09 (0.99-1.20)	.07		1584	1.07 (0.96-1.20)	.20	
Race				.44				.23
Black	1460	1.14 (1.06-1.23)	<.001		1461	1.15 (1.05-1.26)	.003	
Nonblack	2068	1.08 (1.02-1.16)	.02		2072	1.05 (0.97-1.14)	.23	
Age, y				.14				.13
<60	1759	1.11 (1.04-1.19)	.001		1760	1.10 (1.02-1.19)	.02	
≥60	1769	1.08 (1.00-1.16)	.04		1773	1.06 (0.97-1.15)	.20	
Diabetes status				.52				.74
Diabetes	1674	1.11 (1.05-1.17)	<.001		1677	1.09 (1.02-1.16)	.01	
No diabetes	1854	1.10 (1.00-1.21)	.06		1856	1.07 (0.94-1.21)	.33	
History of CVD				.50				.29
CVD history	1135	1.12 (1.05-1.20)	<.001		1138	1.09 (1.01-1.18)	.02	
No CVD history	2393	1.08 (1.00-1.17)	.05		2395	1.09 (0.99-1.19)	.08	
	Myocardial Infarction				Stroke			
Overall	3540	1.07 (0.98-1.16)	.11		3542	1.16 (1.05-1.28)	.003	
Sex				.68				.97
Men	1951	1.06 (0.96-1.17)	.23		1950	1.15 (1.02-1.30)	.02	
Women	1589	1.13 (0.96-1.34)	.14		1592	1.20 (0.98-1.47)	.08	
Race				.30				.69
Black	1468	0.99 (0.85-1.15)	.88		1472	1.22 (1.05-1.42)	.01	
Nonblack	2072	1.10 (0.99-1.21)	.07		2070	1.10 (0.94-1.29)	.24	
Age, y				.66				.79
<60	1766	1.11 (0.98-1.25)	.10		1767	1.17 (1.02-1.34)	.03	
≥60	1774	1.05 (0.93-1.18)	.42		1775	1.15 (0.98-1.34)	.09	
Diabetes status				.64				.98
Diabetes	1682	1.08 (0.98-1.19)	.11		1684	1.17 (1.05-1.32)	.006	
No diabetes	1858	1.03 (0.86-1.23)	.74		1858	1.13 (0.93-1.36)	.21	
History of CVD				.74				.89
CVD history	1140	1.09 (0.98-1.21)	.10		1140	1.19 (1.05-1.35)	.005	
No CVD history	2400	1.04 (0.90-1.21)	.59		2402	1.08 (0.91-1.29)	.38	

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio.

<sup>a</sup> Adjusted for age, sex, race, clinic site, education, waist circumference, lean body mass index, body mass index, cigarette smoking, alcohol drinking, physical activity, low-density lipoprotein cholesterol, glucose, history of CVD, antidiabetic medications, lipid-lowering medications, diuretics, renin-angiotensin system blocking agents, other antihypertensive medications, urinary creatinine excretion, and baseline estimated glomerular filtration rate.

<sup>b</sup> Calibrated to mean urinary creatinine excretion of 1569 mg/24 hours in men and 1130 mg/24 hours in women.

<sup>c</sup> Composite CVD is defined as congestive heart failure, stroke, and myocardial infarction.

increase in calibrated urinary sodium and the CVD outcomes of interest (eTable 2 in the Supplement).

Baseline characteristics of CRIC participants by quartile of calibrated 24-hour urinary potassium excretion are presented in eTable 3 in the Supplement. In unadjusted analyses, higher calibrated urinary potassium excretion was significantly associated with cumulative incidence of composite CVD (cumulative incidence at median follow-up of 28.2% in highest quartile compared with 17.2% in lowest quartile; log-rank  $P < .001$ ) and CHF (cumulative incidence of 21.1% in

highest quartile compared with 11.9% in lowest quartile; log-rank  $P = .03$ ), but not significantly associated with MI (cumulative incidence of 9.7% in highest quartile compared with 7.2% in lowest quartile; log-rank  $P = .08$ ) or stroke (cumulative incidence of 5.7% in highest quartile compared with 3.1% in lowest quartile; log-rank  $P = .50$ ) (eFigure 2 and eTable 4 in the Supplement). Higher calibrated potassium excretion was associated with composite CVD, CHF, and stroke after adjustment for age, sex, race, and clinic site (eTable 4), but after full multivariable adjustment, calibrated potassium



excretion was no longer associated with any of the outcomes of interest. Spline analysis showed a significant linear association with composite CVD ( $P$  for linearity = .048) and CHF ( $P$  for linearity = .03), but no evidence of an association between urinary potassium excretion and MI or stroke (eFigure 3 in the Supplement).

In a sensitivity analysis of spline regression using alternate numbers of knots and middle knot locations, the associations between 24-hour urinary sodium excretion and cardiovascular disease were consistent (eTable 5 in the Supplement).

## Discussion

To our knowledge, this study is the first to investigate the association between sodium excretion and CVD incidence in a population with CKD. These analyses documented a significantly increased risk of CVD in individuals with the highest urinary sodium excretion independent of several important CVD risk factors, including use of antihypertensive medications, baseline eGFR, and history of CVD. Findings were consistent across subgroups and independent of further adjustment for total caloric intake and systolic blood pressure. However, CVD risk was not significantly different among participants with a urinary sodium excretion of 4547 mg/24 hours or less. These findings, if confirmed by clinical trials, suggest that moderate sodium reduction among patients with CKD and high sodium intake may lower CVD risk.

Very limited prior research on the association of dietary sodium with the risk of CVD in patients with impaired kidney function has been conducted.<sup>13,14</sup> Dong et al<sup>13</sup> reported an increase in risk of CVD mortality in those with the lowest mean sodium intake measured from a 3-day diet record among 305 Japanese peritoneal dialysis patients in a retrospective cohort study. Using data from 2 clinical trials investigating the efficacy of angiotensin receptor blockers (ARBs) on kidney outcomes in patients with type 2 diabetes and overt proteinuria, Lambers Heerspink et al<sup>14</sup> conducted a post hoc analysis and found that among those with lower sodium excretion, ARBs were more effective at decreasing kidney and CVD risk. These findings from previous studies, conducted in either a retrospective cohort of peritoneal dialysis patients or in clinical trial participants with diabetes and overt proteinuria, are not directly applicable to patients with CKD in the general population. In contrast, the CRIC Study is a large cohort of diverse participants with CKD that was designed to investigate risk factors for CVD in those with CKD. Therefore, this study should provide an estimate of the association between dietary sodium intake and CVD incidence that is more applicable to those with CKD in the general population.

The results of this study provide evidence of a positive relationship between urinary sodium excretion and clinical CVD with individuals having the highest sodium excretion at the greatest risk of CVD events. Prior work has reported mixed results on the nature of the association between dietary sodium and CVD. Some prior studies have found a positive association between dietary sodium intake and risk of CVD,

coronary heart disease, CHF, and stroke,<sup>9-11,23,24</sup> while others have reported an inverse or J-shaped association between dietary sodium intake and CVD events.<sup>7,8,25-27</sup> The findings in this analysis as a whole support a positive association between urinary sodium excretion and CVD, which is particularly strong in individuals with the highest urinary sodium excretion.

Several methodologic limitations have been described that might account for the inconsistent findings in the sodium-CVD association, including measurement error in dietary sodium intake, confounding, and collinearity of nutritional explanatory variables.<sup>6,28</sup> To address these limitations, this study used repeated 24-hour urine samples. If conducted properly, 24-hour urine collection for sodium excretion is considered the most accurate method of estimating dietary sodium intake at the individual level. It was estimated that approximately 90% of consumed sodium is absorbed and excreted in the urine, and the correlation between measured dietary sodium intake and urinary sodium excretion was more than 0.75.<sup>6,15</sup> The CRIC Study also has well-quantified data on a large number of potential confounding factors that were adjusted in these analyses. In addition, the correlations of urinary sodium excretion with potential nutritional explanatory variables, including urinary potassium excretion ( $r = 0.36$ ) and total calorie intake ( $r = 0.08$ ), were not very strong in the study sample.

The findings reported here were independent of adjustment for systolic blood pressure, suggesting other mechanisms may play a role in the effect of dietary sodium on CVD in CKD patients with high proportions of treated blood pressure. This is consistent with previous findings of a positive association between dietary sodium and CVD independent of blood pressure.<sup>10,23,24</sup> Some possible mechanisms for the direct effects of dietary sodium intake on CVD include endothelial dysfunction,<sup>29</sup> increased oxidative stress leading to vascular damage,<sup>30</sup> insulin resistance,<sup>31</sup> and direct effects on renin-angiotensin-aldosterone system activity.<sup>32</sup>

This analysis found no significant association between urinary potassium excretion and CVD after multivariable adjustment. Prior work in the general population has found a protective effect of dietary potassium on CVD risk,<sup>33</sup> but to our knowledge, the association between potassium intake or excretion and incident CVD has not been investigated in individuals with CKD. The nature of the associations of dietary potassium intake and excretion with CVD in patients with CKD is challenging to understand as a result of abnormal potassium homeostasis and the confounding effect of medications, such as renin-angiotensin-aldosterone blockers.<sup>34</sup> There is also some uncertainty in the degree to which urinary potassium excretion represents dietary potassium intake, particularly in patients with impaired kidney function.<sup>35</sup> In addition, dietary potassium restriction is often advised for those with impaired kidney function.<sup>36</sup> Further research is needed to better understand the association between potassium intake, potassium excretion, and risk of CVD in those with CKD.

This study should be interpreted in light of several limitations. First, it was not possible to compare clinical outcomes among patients with urinary sodium excretion less than 2300 mg sodium/day or less than 1500 mg sodium/day, which are the recommended low sodium targets in the general popu-

lation and in patients with CKD,<sup>6,37</sup> because of very small sample sizes among these subgroups. Second, only three 24-hour urinary specimens were collected, which might not be enough to accurately reflect habitual intake and could underestimate the associations of interest due to regression dilution bias.<sup>38</sup> Third, while many potential confounding factors were adjusted, significant differences across calibrated sodium quartiles were observed for many baseline variables, suggesting confounding by unmeasured or unadjusted factors could be present. Fourth, to our knowledge, the degree to which urinary sodium excretion approximates dietary sodium intake has not been assessed in patients with CKD, whose altered sodium handling by the kidney might affect the intake-

excretion relationship. Fifth, total energy intake had substantial missing values (24%), so it was not adjusted in the primary analyses. However, in a sensitivity analysis, the results did not change significantly after adjustment for total energy intake, although residual confounding could be present due to the possibility of inaccurate total energy quantification based on a single food frequency questionnaire.<sup>39</sup>

## Conclusions

Among patients with CKD, higher urinary sodium excretion was associated with increased risk of CVD.

### ARTICLE INFORMATION

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